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**COMMUNICATION**

# Fast and efficient microwave-assisted synthesis of functionalized peptoids *via* Ugi reactions†‡

**Angélica de Fátima S. Barreto,[a] Otilie E. Vercillo,[a] Mike A. Birkett,[b] John C. Caulfield,[b] Ludger A. Wessjohann[c] and Carlos Kleber Z. Andrade*[a]**

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**A wide range of *N*-alkylglycines (peptoids) can be efficiently prepared *via* Ugi reactions using microwave irradiations. The results confirm the versatility and efficiency of the methodology for the preparation of functionalized peptoids. The products can be used in consecutive Ugi reactions to yield cyclic peptoids of potential biological interest.**

Peptoids, oligomers of *N*-substituted alkyl glycines that mimic the primary natural structure of peptides (Fig. 1),[1–3] are attractive non-natural molecules for drug discovery approaches due to their many biological activities, their facile synthesis, proteolytic stability and wide variety of non-native functionality that can be incorporated into their amide side chains.[1,2] These oligomers can increase cellular permeabilities[3a] and are evaluated as tools to search for biomolecular interactions.[3b,c]

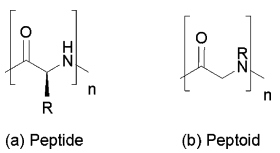



**Fig. 1** Generic structures of a peptide (a) and a peptoid (b).

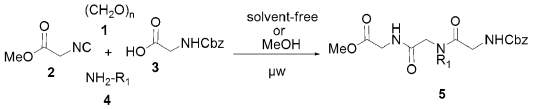
Faster and more efficient methodologies for the synthesis of peptoids need to be explored to improve studies of their biological activities. The synthesis of peptide analogues is also essential to enable a better understanding of structure–activity relationships.

Among several useful reactions, the Ugi four-component reaction (U-4CR)[4] is known to be one of the most versatile tools for the construction of a peptoid backbone. This multicomponent reaction (MCR) easily provides a di-amide by combining four building blocks in one step: an amine, a carboxylic acid, an aldehyde or ketone, called oxo-component, and an isonitrile. MCRs play a significant role on the development of atom-economic and synthetically effective methodologies, which are important goals of synthetic organic chemistry and some of the keys of modern drug discovery.[4,5]

At the same time, the use of microwave (μw) energy to facilitate chemical reactions often results in a dramatic acceleration of reactions, resulting in cleaner outcomes and increased yields.[6,7]

Combining these two versatile tools is a particularly attractive method in current organic synthesis.[8]

Recently, literature has provided many examples of microwave-promoted Ugi reactions.[9,10] Indeed, this reaction can benefit significantly from μw irradiation since it proceeds *via* relatively polar intermediates, which might interact with the microwaves. The solid phase microwave-assisted synthesis of peptoids has already been studied.[11] However, except for a single first and specialized example by one of us,[10a] the microwave-assisted synthesis of peptoids by Ugi reactions is unexplored. Thus, as a continuation of our research on MCRs,[5a,b] we decided to investigate the use of microwave heating in these reactions for peptoid synthesis (Scheme 1).




**Scheme 1** Microwave-assisted Ugi reactions.

Methyl isocyanoacetate **2** (a glycine building block), paraformaldehyde **1**, Cbz-glycine **3**, and several different amines were put together on a microwave reactor (CEM Co., Discover) at 45 °C, subjected to a potency of 150 W and monitored by TLC. For a green, economic and facile synthesis, the use of eco-friendly solvent or ideally solvent-free conditions can be combined with energy-efficient microwave heating. Thus, two different sets of conditions (with and without solvent) were investigated. Overall, the solvent-free combination offered reaction times and yields comparable to conditions using a solvent (Table 1).

To evaluate the efficiency of our method as compared to the usual conditions, compounds **5b** and **5h** were prepared in solution at 45 °C (oil bath), in the absence of μw irradiation (method C). After 18 h, the yields of the products were 78% and 52%, respectively. Using the μw approach, the yields are higher

[a]*Laboratório de Química Metodológica e Orgânica Sintética (LaQMOS), Instituto de Química, Universidade de Brasília, C.P. 4478, 70910-970, Brasília, DF, Brasil. E-mail: ckleber@unb.br; Fax: +55(61) 32734149; Tel: 31073861*

[b]*Centre for Sustainable Pest and Disease Management, Biological Chemistry Department, Rothamsted Research, Harpenden, Hertfordshire, UK, AL5 2JQ*

[c]*Department of Bioorganic Chemistry, Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120, Halle, (Saale), Germany*

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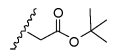
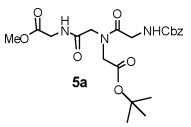
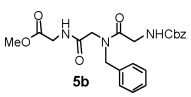
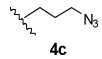
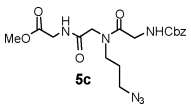
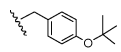
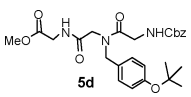
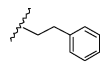
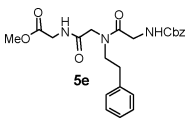
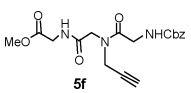
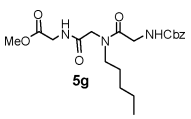
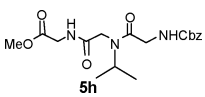
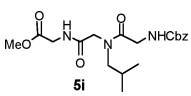
‡ Electronic supplementary information (ESI) available: Experimental details and spectra of selected for compounds. See DOI: 10.1039/c1ob05471f

**Table 1** Microwave-assisted Ugi reactions

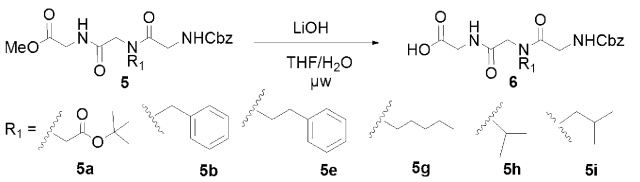
| Entry | *Amine* ($R_1$) | Peptoid | Method[b]/Time | Yield[c] |
|---|---|---|---|---|
| 1[a] |  4a |  5a | A: 2 min<br>B: 4 min | 80<br>77 |
| 2 |  4b |  5b | A: 30 s<br>B: 1 min<br>C: 18 h | 87<br>88<br>78 |
| 3 |  4c |  5c | A: 3 min<br>B: 2 min | 92<br>81 |
| 4 |  4d |  5d | A: 2 min<br>B: 4 min | 79<br>74 |
| 5 |  4e |  5e | A: 2 min<br>B: 6 min | 87<br>81 |
| 6 |  4f |  5f | A: 1 min<br>B: 4 min | 77<br>78 |
| 7 |  4g |  5g | A: 3 min<br>B: 5 min | 84<br>91 |
| 8 |  4h |  5h | A: 2 min<br>B: 3 min<br>C: 18 h | 89<br>88<br>52 |
| 9 |  4i |  5i | A: 2 min<br>B: 3 min | 90<br>90 |

[a] 1 equivalent of $Et_3N$ was used (amine hydrochloride). [b] Method A: 0.5–3 min, 150 W, 45 °C, MeOH as solvent; Method B: 1–6 min, 150 W, 45 °C, solvent-free; Method C: 45 °C, 18 h, MeOH as solvent. [c] Isolated yields of the chromatographically pure products.

and – most important – the reaction times are much shorter (Table 1, entries 2 and 8, respectively).

Aromatic amines substituted either with electron withdrawing or electron donating groups, such as aniline (5 min, 72%), *m*-anisidine (5 min, 70%), and *p*-nitroaniline (6 min, 51%), also reacted in short reaction times and furnished the products in moderate to good yields using method B.

**Table 2** Results of the microwave-assisted ester hydrolysis of some peptoids




| Entry | Reagent | Product | Time (min) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **5a** | **6a** | 3 | 94 |
| 2 | **5b** | **6b** | 3 | 93 |
| 3 | **5e** | **6e** | 4 | 92 |
| 4 | **5g** | **6g** | 3 | 96 |
| 5 | **5h** | **6h** | 3 | 96 |
| 6 | **5i** | **6i** | 5 | 98 |

[a] Isolated yields of the chromatographically pure products.

Spectral analysis of **5a–i** supported the success of the μw-mediated quadruple one-pot condensation. The isolated products were characterized on the basis of $^1$H and $^{13}$C NMR spectroscopy, and high resolution mass spectra. The most important characteristics of the $^1$H NMR spectra of these compounds are the NH peaks between 5.5 and 7.1 ppm and the three methylene groups around 4.1–4.4 ppm. The $^{13}$C NMR spectra corroborated the analysis of the compounds, showing four peaks corresponding to the carbonyl groups (155–170 ppm).

To check the possibility to perform consecutive Ugi reactions (as described by our research group in the synthesis of cyclic RGD pentapeptoids),[5a] using microwave irradiation, we performed the hydrolysis of some peptoids using lithium hydroxide in THF and water. The hydrolysis mixture was irradiated for 3–4 min (150 W) under magnetic stirring and the temperature raised to 60 °C. The reaction conditions are specified in Table 2.

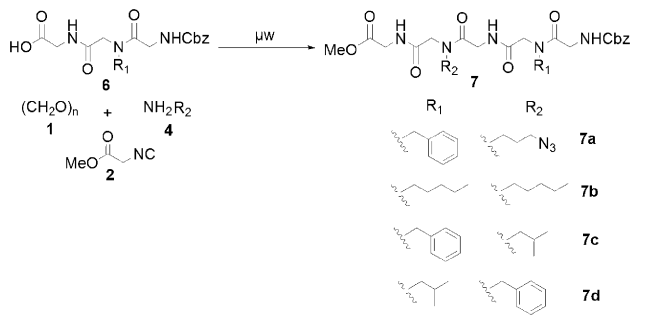
After hydrolysis of esters **5b**, **5g** and **5i**, the resulting acids **6** were used in a subsequent Ugi reaction with paraformaldehyde, a second amine and methyl isocyanoacetate to give esters **7** in high yields after 3–5 min (45 °C, 150 W, method B) of microwave irradiation (Table 3).

The precursor amino acid for the cyclization was obtained after ester hydrolysis of **7b** under our previously described conditions, providing acid **8** in 90% yield (Scheme 2). The *Cbz* protecting group was removed[12] in the presence of 10% Pd–C and ammonium formate in just 5 min (120 °C, 150 W), providing the amino acid **9** in 88% yield, which was cyclized *via* Ugi reaction with paraformaldehyde and *t*-butyl isocyanide under conditions of pseudo-dilution, *i.e.* very slow addition of the bifunctional building block **9**, to prevent oligomerization. The resulting residue was purified by reverse phase flash chromatography, furnishing the cyclic peptoid **10** in 69% yield (Scheme 2).

For a rapid extension and in an attempt to modify peptoids and synthesize new, crosslinked peptide analogues, we decided to join two peptoid backbones by a click reaction incorporating a triazole moiety.

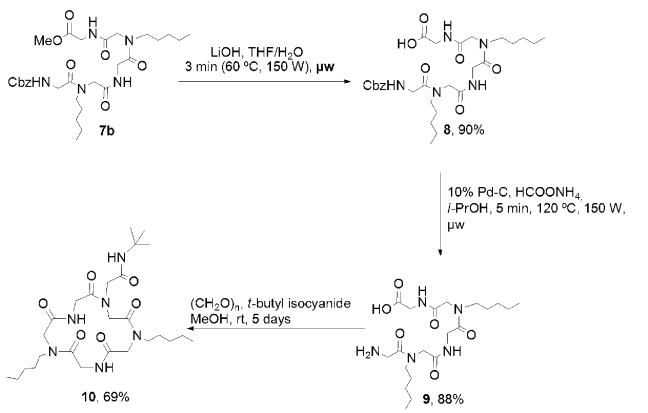
The synthesis of modified peptoids by click chemistry has already been demonstrated, but the peptoids were synthesized by the standard submonomer-approach on solid phase.[13] For our purpose, linear peptoids were synthesized which possess

**Table 3** Results of consecutive Ugi reactions




| Entry | Acid | Amine | Product | Time (min) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **6b** | **4c** | **7a** | 3 | 86 |
| 2 | **6g** | **4g** | **7b** | 5 | 81 |
| 3 | **6b** | **4i** | **7c** | 4 | 92 |
| 4 | **6i** | **4b** | **7d** | 4 | 89 |

[a] Isolated yields of the chromatographically pure products.

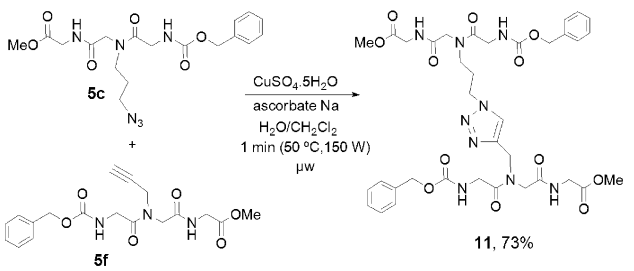



**Scheme 2** Synthesis of cyclopeptoid **10**.

Huisgen-Click reactive groups at specific side chain positions that in principle are easily addressable by Ugi reactions using the appropriate building block. The azide or alkyne functional groups were incorporated as shown in Scheme 1, using 1-azido-3-aminopropane **4c** or propargylamine **4f** as amino components.

The linear peptoids **5c** and **5f** obtained were submitted to Cu(I)-catalyzed azide-alkyne [3 + 2] cycloaddition reaction.[14] For a complete reaction only 1 min of microwave irradiation (50 °C, 150 W) was sufficient in the presence of copper sulfate pentahydrate, sodium ascorbate, and water in dichloromethane as solvent. Product **11** was obtained in 73% isolated yield (Scheme 3). For comparison, the reaction was also conducted without μw at room temperature, stirring for 18 h and the yield decreased to 63%.

We have demonstrated a rapid and direct method to produce functionalized peptoids in good to excellent yields by a simple and efficient route using a one-pot, four-component Ugi synthesis with microwave heating. The procedure offers several advantages including freedom from solvent requirement for the main reaction, operational simplicity, and increased safety for small-scale high-speed synthesis. All this makes the process useful and attractive. Compounds **5a–i** are versatile multifunctional intermediates that




**Scheme 3** Peptoid crosslinking by microwave-assisted "click chemistry".

can be further functionalized at the *N*-Cbz moiety as some of us have shown previously.[5a] Moreover, some peptoids but surely the method itself may prove to be of interest for biological applications.

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